REMARKS

I. Status Summary

Claims 1-17 are pending in the present U.S. patent application and have been examined.

The specification has been objected to for the presence of an embedded hyperlink or other browser-executable code on page 97.

Claims 1-17 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the specification does not reasonably provide enablement for a method of screening for susceptibility to sub-optimal norepinephrine (NE) transport in a subject.

Claims 1-3, 6-7, 13, and 16-17 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are obvious over Jacob *et al.* (Circulation, Vol. 99, pp. 1706-12, 1999; hereinafter "Jacob") in view of Jonsson *et al.* (Psychiatry Research, Vol. 79, pp. 1-9, 1998; hereinafter "Jonsson"). Claims 1, 3, 6-13, and 17 have also been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are obvious over Stober et al. (American Journal of Medical Genetics, Vol. 67, pp. 523-532, 1996; hereinafter "Stober") in view of Jacob.

Claims 1 and 8 have been amended. Support for the amendments can be found throughout the specification as filed, including particularly at page 11, lines 10-22. No new matter has been added as a result of the amendments. Reconsideration of the application as amended and based on the arguments sets forth herein below is respectfully requested.

II. Objection to the Specification

The specification has been objected to for the presence of an embedded hyperlink or other browser-executable code on page 97. In response to this objection, applicants have amended the specification to remove the hyperlink. As a result, applicants respectfully submit that the objection has been addressed, and respectfully request that the objection be withdrawn.

III. *Claim Rejections under 35 U.S.C. § 112, First Paragraph*

Claims 1-17 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the specification does not reasonably provide enablement for a method of screening for susceptibility to sub-optimal norepinephrine (NE) transport in a subject. After careful consideration of the rejection and the Patent Office's bases therefor, applicants respectfully traverse the rejection and submit the following remarks.

According to the United States Patent and Trademark Office (hereinafter "the Patent Office"), the claims broadly encompass screening for susceptibility to sub-optimal NE transport by detecting a polymorphism in the NE transporter (NET) gene. The Patent Office asserts that the specification

> does not establish a statistically significant association with any of the disclosed mutations in the NET gene with the susceptibility to sub-optimal NE transport (except for the A457P mutation in exon 9 in orthostatic intolerance), that would establish all mutations or polymorphisms result in the susceptibility to sub-optimal NE transport. Further, to date, no teaching is available in the art with regards to a universal correlation between any mutation in the NET gene and an association with any general or specific susceptibility to NE transport. It is apparent from the prior art that the unpredictability is high and the instant specification fails to teach any particular mutation associated with the susceptibility to sub-optimal NE transport.

Official Action at page 5. However, no specific scientific or other factual basis in support of this contention has been presented in either the Official Action. Rather, the Patent Office has offered only a series of conclusory statements, contending that "given the broad scope of the claims, the specification does not provide any specific example that would easily predict a significant association of a polymorphism in the NET gene with general susceptibility to sub-optimal NE transport". Official Action at page 5. The Patent Office concedes, however, that the specification is enabling for a method of screening for susceptibility to sub-optimal NE transport in orthostatic intolerance (OI). Thus, it appears that the Patent Office is drawing a distinction between susceptibility to sub-optimal NE transport in OI with a general susceptibility to

sub-optimal NE transport, a distinction that applicants respectfully submit is unwarranted and improper.

Applicants respectfully submit that the specification as filed broadly enables a method for screening for sub-optimal NE transport in a subject, and further that the disclosure that enables the method in subjects with OI is equally applicable to subjects otherwise suspected of suffering from sub-optimal NE transport. The method is not limited to subjects with OI, as there is no characteristic or condition associated with OI that uniquely limits the method to only those patients. If, as the Patent Office concedes, the method is enabled for OI patients (who, applicants wish to point out, are exemplary "subjects"), applicants respectfully submit that the method can be applied to other subjects without modification. Consequently, applicants respectfully submit that the Patent Office has created an artificial distinction between subjects that are OI patients and subjects generally that is not supported by any scientific reasoning.

Furthermore, applicants respectfully submit that 35 U.S.C. §112, first paragraph, requires no more than a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims, and this requirement has clearly been met. For example, the specification discloses SEQ ID NOs: 1 and 2, which are the nucleotide and amino acid sequences, respectively, of the human NET gene and gene product. The "MATERIALS AND METHODS USED IN EXAMPLES" section of the specification also discloses techniques that can be used to isolate and characterize NET nucleic acids from a subject in order to identify polymorphisms in any exon of the NET coding sequence (*see* the subsection entitled Detection of Mutations). Once polymorphisms have been identified, the specification of the instant application teaches assays that can be used for determining whether or not a polypeptide encoded by the polymorphic NET nucleic acids would be expected to result in sub-optimal NE transport (*see e.g.* the section of the Examples entitled Functional Analysis of Identified Coding Mutation). Applicants respectfully submit that the Chinese hamster ovary transfection assay used to test the A457P polymorphism can be adapted for testing any nucleic acid sequence encoding a polymorphic NET polypeptide using techniques known to one of ordinary skill in the art. Furthermore,

the specification discloses various pharmacological tests that can be performed on subjects that can be used as further evidence of *in vivo* sub-optimal NET function (*see e.g.* the section entitled Other Diagnostic Methods beginning on page 81).

Summarily, applicants respectfully submit that the specification as filed teaches techniques that can be used for identifying nucleic acids encoding polymorphic NET polypeptides present in subjects, and further for assaying the NE transport activities of these polypeptides to identify polymorphisms that cause sub-optimal NE transport. Accordingly, applicants respectfully submit that the current rejection of claims 1-17 under 35 U.S.C. § 112, first paragraph, has been addressed. Applicants respectfully request the withdrawal of the instant rejection.

IV. Claim Rejections under 35 U.S.C. § 103(a)

IV.A. Rejection over Jacob in view of Jonsson

Claims 1-3, 6-7, 13, and 16-17 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Jacob in view of Jonsson. Applicants have carefully reviewed the instant rejection and the Patent Office's assertions related to the rejection, and respectfully traverse the rejection for the reasons presented hereinbelow.

The Patent Office's basis for the instant rejection can be summarized as follows: the Patent Office asserts that Jacob teaches a method of screening for susceptibility to sub-optimal NE transport in OI patients, but concedes that Jacob does not teach NET polymorphisms. According to the Patent Office, this defect is cured by Jonsson, which the Patent Office contends teaches a method for screening for susceptibility to sub-optimal NE transport by detecting a polymorphism of a NET gene in a biological sample obtained from a human subject. From this, the Patent Office asserts that it would have been prima facie obvious to a person of skill in the art at the time the invention was made to modify a method of detecting, correlating, or associating abnormal NE transport with OI as asserted to be taught by Jacob with a method for detecting NET gene polymorphisms as asserted to be taught by Jonsson in order to develop a sensitive and improved method for detecting susceptibility of a subject to OI because Jonsson "taught a possible association between NE transporter

gene polymorphism and differential regulation of NE transport or turnover rate". Official Action at page 8.

Initially, with respect to the Jacob reference, applicants respectfully disagree with the Patent Office's characterization of the teachings of Jacob. Claim 1 recites a method of method of screening for susceptibility to sub-optimal norepinephrine (NE) transport in a subject comprising (a) obtaining a biological sample from the subject; and (b) detecting a polymorphism of a NE transporter gene encoding an amino acid change in the biological sample from the subject, the presence of the polymorphism indicating the susceptibility of the subject to sub-optimal norepinephrine transport. Jacob, on the other hand, discloses testing a biological sample not for a polymorphism in the NET gene, but for alterations in the presence of certain markers of NE spillover and clearance.

Thus, at best Jacob discloses a method for detecting evidence of alterations in NE spillover and clearance. While abnormal NET function might explain the observations made in Jacob, many additional explanations are believed to be possible. In particular, Jacob itself discloses several other mechanisms by which alterations in NE spillover and clearance can result. According to Jacob:

> a decrease in norepinephrine clearance could be due to a decrease in cardiac output resulting from pooling of blood in the lower extremities, hypovolemia, a reduction in liver blood flow, or a combination of these mechanisms...

Jacob at page 1710 (citations omitted). Applicants further submit that Jacob disclosed additional potential causes of alterations in NE spillover and clearance in OI patients, including decreased norepinephrine stores in neurons (page 1710) and distorted architecture of the synapse (page 1711).

Thus, applicants respectfully submit that Jacob presents no more than a laundry list of potential explanations for alterations in NE spillover and clearance, and provides no suggestion of how to identify the cause or causes of the defects. As a result, applicants respectfully submit that Jacob cannot be read to provide one of ordinary skill in the art with a reasonable expectation of success in finding polymorphisms in NET that correlate with sub-optimal NE transport. In fact, no reference has been cited that

teaches any association between sub-optimal NE transport and an NET polymorphism that results in an amino acid change, as this association can only be found in the specification of the instant patent application. Accordingly, applicants respectfully submit that Jacob cannot be read to teach the presently claimed method as asserted by the Patent Office without the use of hindsight vision based on the disclosure of applicants' specification

The Jonsson reference does not support the deficiencies of Jacob. Applicants respectfully submit that the cited Jonsson reference does not teach a possible association between NE transporter gene polymorphisms and differential regulation of NE transport or turnover rate that can be associated with a change in the amino acid sequence of an NET polypeptide encoded by the NET transporter gene. Careful review of the Jonsson reference reveals that Jonsson studied a silent polymorphism, meaning that the nucleic acid polymorphism disclosed in Jonsson did not result in any amino acid change in the NET polypeptide encoded by the NET gene. Thus, applicants respectfully submit, and the Jonsson reference itself concedes, that the polymorphism studied was non-functional (*i.e.* did not change the amino acid sequence of the NET polypeptide itself). Applicants respectfully submit that Jonsson even suggests that the effects on constituents of cerebrospinal fluid observed may have nothing whatsoever to do with the NET gene when it states on page 6 that "it is possible that the non-functional NET polymorphism investigated is in linkage disequilibrium with a yet unidentified functional polymorphism in the NET gene or another gene in the proximity". As such, applicants respectfully submit that Jacob in view of Jonsson presents no more than an "ought to be tried" scenario that cannot be used to establish a prima facie case of obviousness.

Summarily, applicants have amended claims 1 and 8 to recite detecting a polymorphism of a NE transporter gene encoding an amino acid change in a biological sample from the subject. Neither Jacob nor Jonsson alone or in combination teaches or suggests this element, and thus applicants respectfully submit that a prima facie case of obviousness has not been presented. Claims 2-3, 6-7, 13, and 16-17 all depend directly or indirectly from distinguished claim 1, and thus also include this

element. As a result, applicants respectfully submit that these claims have also been patentably distinguished from the cited references. Accordingly, applicants respectfully request that the rejection of claims 1-3, 6-7, 13, and 16-17 under 35 U.S.C. § 103(a) over Jacob in view of Jonsson be withdrawn,

IV.B. Rejection over Stober in view of Jacob

Claims 1, 3, 6-13, and 17 have also been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are obvious over Stober in view of Jacob. According to the Patent Office, Stober teaches the methods of claims 1 and 17, wherein NET gene polymorphisms are detected and susceptibilities to sub-optimal NE transport are analyzed. After careful consideration of the rejection and the Patent Office's basis therefor, applicants respectfully traverse the rejection and submit the following comments.

The Patent Office asserts that Stober teaches assessing an association between the presence of an NET gene polymorphism and NE transport. The Patent Office concedes, however, that Stober does not teach the presence of a polymorphism in the NET as an indication of the susceptibility of the subject to sub-optimal NE transport. The Patent Office asserts that this defect is cured by Jacob, which is asserted to teach the method of claim 2. By combining the asserted teachings of these two references, the Patent Office contends that it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to combine a method of detecting a polymorphism in the NET gene as asserted to be taught by Stober with determining abnormal NE clearance in OI as taught by Jacob to

> achieve expected advantage of developing a sensitive method for detecting susceptibility of a subject to sub-optimal NE transport because Jacob et al. taught that "impairment in the norepinephrine transporter could be responsible for the decreased norepinephrine spillover observed in the OI patients and the role of norepinephrine transporter function in the dramatic abnormalities in catecholamine clearance must receive increased attention".

Official Action at page 10 (citations omitted).

Initially, applicants respectfully traverse the Patent Office's assertion that Stober teaches assessing an association between the presence of an NET gene

polymorphism and NE transport. A careful reading of Stober clearly indicates that no pharmacological or biochemical tests were performed to assess NE transport, and thus there can be no teaching in the cited reference of an association between NET polymorphisms and NE transport. Rather, Stober attempts to correlate NET polymorphisms and certain psychiatric illnesses such as schizophrenia and bipolar affective disorder, and no such correlation was found. Applicants respectfully submit that as such, it is only by using the knowledge collected from the instant specification combined with hindsight vision that the Patent Office can assert that Stober associates NET polymorphism with NE transport.

The deficiencies of the Stober reference are not supported by the Jacob reference. Applicants direct the Patent Office's attention to the discussion of the Jacob reference hereinabove and incorporated by reference herein pointing out the deficiencies in the teachings of the Jacob reference. As discussed in more detail hereinabove, Jacob discloses testing a biological sample not for a polymorphism in the NET gene, but for alterations in the presence of certain markers of NE spillover and clearance. Thus, at best Jacob discloses a method for detecting evidence of alterations in NE spillover and clearance.

Furthermore, applicants respectfully submit that independent claim 1 recites a method of screening for susceptibility to sub-optimal NE transport in a subject by (a) obtaining a biological sample from the subject; and (b) detecting a polymorphism of a NE transporter gene encoding an amino acid change in the biological sample from the subject, the presence of the polymorphism indicating the susceptibility of the subject to sub-optimal norepinephrine transport. Applicants respectfully submit that the Patent Office has not established that the combination of references teaches each and every element of the claims, and in fact concedes that they do not. First, on page 10, the Patent Office concedes that Stober does not teach the presence of a polymorphism in the NET gene as an indication of the susceptibility of the subject to sub-optimal NE transport. Second, the Patent Office concedes on page 7 that Jacob does not teach polymorphisms in the NE transporter gene, and thus applicants respectfully submit that Jacob cannot be read to cure the defect conceded in Stober. Since neither Stober

nor Jacob can be read to disclose or suggest that the presence of a polymorphism in the NET gene is an indication of the susceptibility of the subject to sub-optimal NE transport, applicants respectfully submit that it is only by using impermissible hindsight vision that the Patent Office has combined the cited references to arrive at the claimed invention.

Summarily, applicants respectfully submit that when the Jacob and Stober references are taken in their entireties and in context, there is no suggestion that NET gene polymorphisms might be associated with susceptibility to sub-optimal NE transport in a subject, and that it is only with hindsight vision that such a conclusion can be reached. Accordingly, applicants respectfully submit that a prima facie case of obviousness has not been established with respect to claim 1. Claims 3, 6-13, and 17 all depend directly or indirectly from distinguished claim 1, and thus also are believed to have been distinguished from the cited references. Accordingly, applicants respectfully request that the rejection of claims 1, 3, 6-13, and 17 under 35 U.S.C. § 103(a) over Stober in view of Jacob be withdrawn and that the claims be allowed at this time.

CONCLUSIONS

In light of the above Amendment and Remarks it is respectfully submitted that the present application is now in proper condition for allowance, and such action is earnestly solicited.

If any minor issues should remain outstanding after the Examiner has had an opportunity to study the Amendment and Remarks, it is respectfully requested that the Examiner telephone the undersigned attorney so that all such matters may be resolved and the application placed in condition for allowance without the necessity for another Action and/or Amendment.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiencies or credit any overpayments associated with the filing of this correspondence to Deposit Account Number **50-0426**.

Respectfully submitted,
JENKINS, WILSON & TAYLOR, P.A.

Date: 05/24/2004 By: _____

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